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Consent for the diagnosis of preclinical dementia states: a review

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ABSTRACT [247 words]

It is now possible to detect the pathology of Alzheimer's disease (AD) many years before symptoms and signs otherwise become manifest. Biomarkers of disease include evidence of amyloid and tau in the cerebrospinal fluid and neuroimaging which (for instance) allows amyloid in the brain to be visualized. There is, thus, a preclinical state in which it is possible to identify Alzheimer's pathology long before there is clinical evidence of disease. Much research focuses on this preclinical state because it seems likely that treatments will be more effective before the disease is established. This means that researchers can discover Alzheimer's pathology some years before the person is at risk of developing the condition. In memory clinics, too, people may present with early (prodromal) symptoms which do not yet amount to a dementia syndrome (e.g. mild cognitive impairment), yet biomarker evidence that dementia is highly likely to develop. This is problematic because people will be required to consent to the disclosure of findings that indicate an uncertain risk of an alarming disease. We carried out a scoping review of the issues that arise in connection with a "diagnosis" of preclinical dementia. We identified four themes in the literature: stigma; ethical issues; psychological burden; and language. We shall discuss these themes and related issues that emerge to do with meaning, medicalization, virtues and values. More research is now required to understand these issues in detail, where the emphasis should be on the breadth of research, which must be biopsychosocial and ethical.

Keywords:

Alzheimer's disease
Biomarkers
Consent
Dementia
Ethics
Preclinical diagnosis

Consent for the diagnosis of preclinical dementia states: a review

1. Introduction

Within the last ten years, new concepts for understanding Alzheimer's disease (AD) have emerged [1,2]. Although these concepts differ in detail and are still evolving, there is general agreement that AD is a continuum from a preclinical state via a prodromal condition to full-blown Alzheimer's dementia.

Alzheimer's dementia is the well-recognized condition in which there is an acquired global impairment of cognitive function which is severe enough to affect activities of daily living, aspects of personality and behaviour, where the typical Alzheimer's pathology can be demonstrated post-mortem. Concepts such as mild cognitive impairment (MCI) emerged subsequently to describe the (prodromal) state, where limited cognitive impairment did not fulfil the criteria for full-blown dementia and did not affect activities of daily living.

However, not all cases of MCI progress to dementia [3].

The new idea is that of a preclinical state, extending over many years, during which the person is asymptomatic but has detectable pathology. In fact, it has been known for some time that an albeit small group of people (less than 1.5% of those with Alzheimer's dementia) carry a dominant gene for AD and remain pre-symptomatic for many years. The new concept has emerged because it is now technically possible to detect Alzheimer's pathology preclinically. A variety of biomarkers allow much greater (albeit not perfect) accuracy in terms of predicting that a person will develop Alzheimer's dementia because of current asymptomatic pathology. Thus, amyloid (one of the hallmarks of Alzheimer's pathology) can be detected in the brain using both neuroimaging and analysis of the cerebrospinal fluid (CSF). Tau, another protein (like amyloid) found in the brains of people with Alzheimer's dementia, can also be detected in the CSF (and will soon be detectable by neuroimaging). There are other morphological changes in the brain that are more typical of Alzheimer's than

of other dementias. These biomarkers, along with genetic markers for susceptibility such as the ApoE ϵ 4 allele, give meaning to the concept of “non-dementia AD”.

Inasmuch as this is new, therefore, it raises new ethical challenges. For it is now perfectly possible that a researcher will learn that a person has significant Alzheimer’s pathology in the absence of overt symptoms or signs of the disease. This possibility is stimulating ethical interest [4]. We decided to review the literature to consider issues around the identification of preclinical dementia.

2. Methods

2.1 Sources of Information

We searched the databases PubMed, ScienceDirect and PsychSource separately.

2.2 Search terms and parameters

Our search used the terms “asymptomatic at risk for AD”, “asymptomatic AD”, “pre-dementia”, “preclinical dementia”, “presymptomatic AD”, “prodromal AD”, “mild cognitive impairment” and “MCI” each in combination with “consent” AND “diagnosis”.

The search was limited to title and abstract, but any research methodology was accepted including meta-analyses, randomised controlled trials, observational studies, reviews and opinion pieces. The search was further limited to papers written in English, involving humans and published between 2006 and 2016. Age and type of potential dementia were not exclusion criteria. This was a scoping review in which we were concerned with broad topics and a variety of study designs without an intention to address a specific research question and without consideration of the quality of the studies identified [5].

2.3 Selection criteria

Papers included in this review were those specifically concerned with the consent for a diagnosis of pre-dementia states and the surrounding issues regarding disclosure of information and its implications. Papers concerning the consent for a diagnosis of clinical

dementia were excluded; those concerned solely with capacity, screening measures and predictive prognosis were also not considered. We restricted our review specifically to preclinical states.

2.4 Synthesis

After the initial literature search, the papers were read in full by each member of the team. We then met to discuss emergent issues and themes in greater detail. Through our discussions numerous issues emerged; a narrative or descriptive account of the literature coalesced around four main themes.

3. Results [950]

The papers we identified mainly referred to AD, which was therefore the focus of our analysis. After the exclusion of duplicate papers, our search identified ten papers: seven were opinion pieces or non-systematic reviews [6,7,8,10,11,13,15]; three were based on empirical studies [9,12,14], one of which was a Delphi study [9]. The four themes to emerge were: stigma; ethical issues; psychological burden; and language. We shall discuss each theme in turn. However, the themes inevitably overlap.

3.1 Stigma

One significant concern is that preclinical identification of AD will lead to stigma [11,15]. Much of this concern reflects experience and research involving MCI and AD dementia. Stigma may show itself in a variety of forms, from discrimination in the work place to difficulty gaining insurance [8,9,10,15]. There may also be interpersonal stigma [9], public or social stigma [11], involving social isolation and distancing [10,15]. Johnson and Karlawish cite research that shows it is not AD itself that elicits stigma, but ‘the label’s association with expectations of certain future decline’ [10]. They also identify civic rights and privileges, such as driving and voting, as further areas where there might be discrimination [10]. The negative perception of the AD label can become internalised causing self-stigma [7,11].

Stigma can also be directed at those who care for people living with dementia [11]. Worries about stigma have led some to suggest the need for new legislation around privacy and confidentiality [7,8,10]. It would seem unjust that people altruistic enough to participate in research should then find their ability to gain employment or insurance compromised because of findings with uncertain but potentially devastating consequences.

3.2 Ethical issues

Stigma is, of course, an ethical and political issue as well as a social one. Ethical concerns loomed large in the literature, provoked by the ‘prognostic uncertainty and lack of clinical utility’ associated with preclinical identification of AD [9]. Much of the discussion centred on the (uncertain) risks, burdens and benefits of early “diagnosis” [6,11]. To discuss relevant ethical issues, the four principles of medical ethics can be applied [16].

First, research aimed at preclinical identification of AD is predicated on the possibility of *beneficence*: the aim is to do good by treating AD early [6,15]. Interestingly, however, Dubois and colleagues ‘failed to find studies clearly focused on the benefits for patients, carers, or society of a timely diagnosis at the prodromal stage, before dementia sets in’ [11]. One possible benefit of a ‘timely diagnosis’ might be the possibility of advance care planning, end-of-life decision-making, the opportunity to change unhealthy lifestyles and seek better medical care [11]. Certainly, the diagnosis of dementia leads to treatment and support, so similar benefits may follow early identification of AD pathology [15]. Also, people who are known (e.g.) to be negative for cerebral amyloid (based on neuroimaging) will not be used for studies aimed at treating amyloid, which is therefore a benefit to them, just as knowing that you are free of disease is good in general [13].

Secondly, the burdens associated with disclosure of biomarker positivity (i.e. the knowledge that AD pathology is present albeit asymptotically), avoidance of which is a matter of the principle of *non-maleficence*, will necessitate careful psychological preparation and follow-

up [10]. This requirement is likely to diminish over time as therapeutics improve, as has been seen in screening for HIV status [6]. But non-maleficence, avoiding harm, is already used (rightly or wrongly) as an excuse *not* to inform patients of their diagnosis of AD [7]. Many people do not wish to undergo diagnostic testing, ‘perhaps for fear of receiving bad news with little prospect of effective treatment’, but equally ‘some people are willing to pay for diagnostic clarity’ [14].

Several papers mention a consequentialist framework in talking of the ethical issues around disclosure. Thus, diagnostic disclosure may have some utility, but this must be ‘situated in a broader consequentialist framework ... the central premise of which is that one’s approach toward disclosure be grounded in the probable impact the information will have on a given patient’ [7].

In this connection, almost all the papers we reviewed cited the Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) project. Participants in REVEAL, who were told their risk of AD based on ApoE status, were no more likely to develop anxiety, depression or test-related distress than those who received information about their risk of AD solely based on age, family history and gender [17]. At follow-up one year after disclosure, the participants seemed more sensitive both to the limitations around being told their genetic risk and to the possibility of discrimination, but the benefits in favour of testing still strongly outweighed the disbenefits [18]. The importance of disclosing information in an appropriate manner to cognitively normal older people who may nevertheless have AD pathology led Harkins and colleagues, using a Delphi method, to develop a process with ongoing monitoring of mood and safety [9]. As Johnson and Karlawish suggest, the ‘empirical data on the *consequences* of disclosure is important for ethics questions about the *advisability* of disclosure’ [10].

Lim and colleagues undertook a study in which amyloid status, determined by positron emission tomography (PET) scanning, was disclosed to participants [12]. Although 63

healthy older people enrolled in the scanning study, only 11 were willing to know their amyloid status. Only four of these had increased levels of amyloid. The study demonstrated no adverse psychological effects from disclosure and the four with increased amyloid made positive changes to their lifestyles, with more exercise and changes to their diet [12].

Being told whether you are biomarker positive and, therefore, your risk status for AD dementia is also relevant to the third principle of medical ethics, *autonomy*. Telling people *in the right way* about their risks is a matter of showing respect for the individual's autonomy [9]. It is a way of empowering them [15]. Respect for autonomy also underpins the imperative that people should have the capacity to give full consent to studies that lead to disclosures about risk [10,13]. Autonomy is respected by the process of shared decision-making [15]. 'Respect for persons' is a basic requirement for clinical research even where participants lack autonomy [13]. One way to ensure a person's autonomous prior choices are honoured in the context of declining capacity is to consider encouraging the use of 'research advance directives' [10, but also see 19, section 8.44].

Fourthly, there are issues of *justice* [8,15]. There is the common enough issue that large studies are costly and there ought to be some hope of success before they are pursued. Not only will studies use material resources, but if they are also psychologically burdensome for the participants, this should be considered. However, a much weightier consideration is the possibility that such studies, if (but only if) successful, would bring about significant savings in that the onset of dementia could be postponed, its progression could be slowed and potentially it could be cured [8].

3.3 Psychological burden

Worries about inducing anxiety and depression in those to whom their biomarker status is disclosed are commonly mentioned in the literature [6,7,11,13,15]. Psychological burden, or 'existential dread' [20, cited in 6], is not only to do with biomarker disclosure being stressful

at the time, but is also that it will cause ‘fear for the future’ [8], which may worsen [12]. Hence the need to screen for anxiety, depression and distress before, during and after disclosure [8,9]. This is necessary both for research purposes (to learn who is affected etc.) and for therapeutic intervention. In addition, psychoeducation is required to help people deal with the uncertainty surrounding any disclosure of risk and the implications for them and for their families [6,9,12,15].

Comparisons are sometimes made with Huntington’s disease, including over the risk of suicide [13], where suicide is seen as a consequence of the psychological burden that follows disclosure [11]. Molinuevo and colleagues suggest that the main risks of disclosure, ‘include placing a cloud of uncertainty over participants that affect their daily lives ...’ [13]. Knowing your biomarker status early means that you have a longer period of burdensome uncertainty. Molinuevo and colleagues also suggest that disclosure should not occur in observational studies, unless the studies are of the impact of disclosure, because the only effect is to cause uncertainty; whereas disclosure in intervention studies is necessary and protects those who are unlikely to benefit from treatment [13].

3.4 Language

The need for good communication – communication that allows some sort of clarity despite the ambiguity of diagnostic terms that relate to ‘disease defined by a dimensional risk of impairment rather than a categorical pathology’ [10] – is central to the theme of language [6,7,13]. Good communication requires accurate, unambiguous information [9,12]. It also requires the clinician to be able to determine whether or not the person wishes to know the information [15]. But the theme goes further. The choice of words is not solely about clear communication; it is also about decision-making on a broader scale involving all concerned [15]. And it is about our concepts of disease: ‘our language for talking about AD will likely change’; instead of AD we may speak about ‘brain amyloidopathy’ [6]. Karlawish continues:

‘And yet, such terms cannot elide an essential fact. They denote a dreaded risk: developing dementia’ [6].

4. Discussion

Inevitably, our review has demonstrated a good deal of ethical concern around the identification of preclinical dementia. Worries about stigma, about the psychological burden of disclosure of biomarker status and about the need for good communication are all driven by ethical concerns. In its recent discussion paper on ethical issues linked to changing definitions in relation to AD, Alzheimer Europe identified notions such as the representation of health and disease, personal identity and personhood, citizenship and equality, amongst others, as worthy of consideration [4]. No doubt our own analysis could be developed further. Our scoping review has limitations. We could have expanded our search terms, e.g. to include ‘disclosure’. We did not search many databases. Concepts such as ‘preclinical dementia’ are relatively new so that the use of these terms is inconsistent and empirical studies infrequent. Nevertheless, several points emerge for further discussion.

First, in the empirical study of the effects of disclosure of amyloid status, Lim and colleagues found reassuring results [12]. But of the 63 eligible, only 11 participated in the study and of these only four showed increased amyloid. So this was a small and selective group. Questions remain concerning the 52 people who were not willing to participate in the study. Whose voices do we hear concerning what is to be regarded as good practice or acceptable research? Molinuevo and colleagues talk of the ‘public’s values’ [13]; but so far we have little idea what these might be. This contrasts with our awareness that most people with AD dementia *do* wish to know their diagnosis [21].

Secondly, a related point concerns the limited range of ethical approaches or theories applied to the issues under consideration. Consequentialism must inevitably give great weight to the possibility of therapeutic advance (if not cure). But neither consequentialism nor the four

principles cover all the relevant moral territory [22]. If we add virtue ethics into the mix, we must then consider prudence (or practical wisdom), fortitude, courage, honesty, charity, diligence, kindness, humility, patience, generosity, fidelity and so on. A more nuanced discussion would need to consider these dispositions in relation to researchers and research participants. It may be that good reasons – prudent, brave, kind reasons – emerge why a person might or might not wish to know his or her risk of AD dementia.

Thirdly, discussion of the virtues suggests a notion of the good life, of what it is to flourish as a human being. Some might see medicalization of many aspects of living as the antithesis of the good life. It can be argued that where there is no dysfunction or disability it is wrong to use the term “disease”. On this view, it does not make sense to speak of “asymptomatic AD”, particularly because AD pathology can be present in normal individuals and will not inevitably determine that someone develops the disease. Biomarker positivity, therefore, need not be regarded as a disease state [23]. To call it such is to encourage a cultural shift that need not occur. A moderate approach might be to suggest that further research is required into just what public values amount to in these debates.

Finally, language suggests meaning. We need to make sure that participants in studies understand what the language of science means and that scientists understand participants’ true concerns. But we also need to understand the individual nature of meaning. Several of the papers in our review mentioned shared decision-making [14,15]. The point about shared decision-making, however, is that both parties in the decision must really hear and understand each other. Their *meanings* must be shared. (Ownership of the information to be shared is another underlying issue we have not discussed [24].) What is important, therefore, is the nature of the individual encounter, whether this be in the clinic or in the research laboratory.

5. Conclusion

Our scoping review of the issues that arise concerning a disclosure of preclinical dementia has identified four themes in the literature: stigma; ethical issues; psychological burden; and language. We have gone on to argue that we need to know more about the values that might be at play here (including the public's values), which will touch on attitudes towards medicalization, on what we regard as normal or as pathological and, consequently, on what counts in the good life. This will require more nuanced analysis of the ethical issues involved and more research to understand these issues in detail, where the emphasis should be on the breadth and depth of research. The importance of the subject and of what is at stake requires an interdisciplinary, biopsychosocial and ethical, quantitative and qualitative approach. As Jason Karlawish put it: 'The discovery of preclinical AD may be how we prevent the tsunami of dementia, but we must not drown in the challenges created by our own discovery' [6].

Word count (text and title): 3000

Authors' contributions

Julian C. Hughes declares that he helped to conceive the form of the review, that he advised on the design of the literature search, that he read the papers identified in the search and was involved in identifying the themes that emerged from the literature, that he wrote most of the initial draft of the paper, oversaw the final draft and that he has seen and approved the final version. He served on the Alzheimer Europe working group that produced 'Discussion paper on ethical issues linked to the changing definitions/use of terms related to AD' [reference 4], but has no other conflicts of interest.

Tom Ingram declares that he helped to conceive the form of the review, that he undertook the literature search, that he read the papers identified in the search and that he was involved in identifying the themes that emerged from the literature, that he contributed to an initial draft

of the paper, contributed to the final draft and that he has seen and approved the final version. He has no conflicts of interest.

Aron Jarvis declares that he helped to conceive the form of the review, that he advised on the design of and participated in the literature search, that he read the papers identified in the search and that he was involved in identifying the themes that emerged from the literature, that he contributed to an initial draft of the paper, contributed to the final draft and that he has seen and approved the final version. He has no conflicts of interest.

Elise Denton declares that she helped to conceive the form of the review, that she advised on the design of the literature search, that she read the papers identified in the search and that she was involved in identifying the themes that emerged from the literature, that she contributed to an initial draft of the paper, contributed to the final draft and that she has seen and approved the final version. She has no conflicts of interest.

Zoe Lampshire declares that she helped to conceive the form of the review, that she advised on the design of the literature search, that she read the papers identified in the search and that she was involved in identifying the themes that emerged from the literature, that she contributed to the final draft of the paper and that she has seen and approved the final version. She has no conflicts of interest.

Cathy Wernham declares that she read the papers identified in the search and that she was involved in identifying the themes that emerged from the literature, that she contributed to an initial draft of the paper, contributed to the final draft of the paper and that she has seen and approved the final version. She has no conflicts of interest.

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Conflicts of interest

Julian C. Hughes served on the Alzheimer Europe working group that produced ‘Discussion paper on ethical issues linked to the changing definitions/use of terms related to AD’ [reference 4], but has no other conflicts of interest. Other authors have no conflicts of interest.

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